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A Meta-Analysis of Risk Factors for Stroke after Spinal Surgery

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Essay

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Abstract

Background: Perioperative stroke is a rare but serious complication of spinal surgery. However, it has been reported that there are multiple risk factors that contribute to postoperative stroke, but still remains controversial. The aim of this study is to investigate the risk factors of stroke after spinal surgery.

Methods: A systematic search of relevant articles is published in PubMed, Embase, Web of Science, Cochrane Library and Clinical Trials databases until August 2022. According to the inclusion and exclusion criteria, two reviewers independently performed literature screening, data extraction and quality assessment of the obtained literature. The Newcastle-Ottawa Scale (NOS) score was used for quality assessment, and STATA 16.0 software was used for meta-analysis.

Results: A total of 1706 relevant articles were initially identified and 13 articles were finally included in this study for data extraction and meta-analysis. The meta-analysis showed that advanced age, hypertension and diabetes mellitus were the risk factors for stroke after spinal operation. The OR values (95%CI) of these three factors were 3.36 (1.81, 6.24), 1.61 (1.26, 2.06) and 2.07 (1.23, 3.49) respectively.

Conclusions: Advanced age, hypertension and diabetes mellitus are the current risk factors for postoperative cerebrovascular accidents (CVA).

Keywords: Stroke; Spine Surgery; Risk Factors; Advanced Age; Hypertension; Diabetes Mellitus

Abbreviations: PRISMA: Preferred Reporting Items For Systematic Reviews And Meta-Analyses; MOOSE: Meta-Analysis Of Observational Studies In Epidemiology; PICOS: Population, Intervention, Criteria, Outcome And Study Design; NOS: Newcastle-Ottawa Scale; TIA: Transient Ischemia; CVA: Cerebrovascular Accidents.

Introduction

With the aging process of people, the incidence rate of spinal degenerative diseases is gradually rising [1,2]. Surgical management should be adopted for the treatment of spinal degenerative diseases when conservative treatment is ineffective for 3 months [3,4]. Spinal surgery can significantly improve patients' neurological function and improve their quality of life, so that they can return to normal life as early as possible [5,6]. However, previous literatures reported that there are many complications (infection, nerve edema, nerve injury, vascular injuries, dural tears, stroke, etc.) after spine surgery [3,7,8]. The stroke was one of the most serious postoperative complications, which could affect the surgical effects and even patient's life. Some literatures have reported that age, hypertension, diabetes mellitus, hyperlipidemia, cerebrovascular disease, etc could affect the incidence of postoperative stroke [9-12]. However, there still remains controversial [10]. Therefore, the aim of this study is to investigate the risk factors of stroke after spinal surgery.

Materials and Methods

Study selection and inclusion criteria

We conducted a systematic search of the scientific literature on perioperative stroke and performed a meta-analysis of the pooled data from the eligible studies. Case-control studies or cohort studies were searched from PUBMED, EMBASE, Web of Science, Cochrane Library and Clinical Trials independently by two authors. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines. Taking PubMed as an example, the specific retrieval strategy is shown as follows: (((((((((((((((((((((Risk Factors[Title/Abstract]) OR (Hazard[Title/Abstract])) OR (dangerous factors[Title/Abstract])) OR (Factor, Risk[Title/Abstract])) OR (Risk Factor[Title/Abstract])) OR (Social Risk Factors[Title/Abstract])) OR (Factor, Social Risk[Title/Abstract])) OR (Factors, Social Risk[Title/Abstract])) OR (Risk Factor, Social[Title/Abstract])) OR (Risk Factors, Social[Title/Abstract])) OR (Social Risk Factor[Title/Abstract])) OR (Health Correlates[Title/Abstract])) OR (Correlates, Health[Title/Abstract])) OR (Population at Risk[Title/Abstract])) OR (Populations at Risk[Title/Abstract])) OR (Risk Scores[Title/Abstract])) OR (Risk Score[Title/Abstract])) OR (Score, Risk[Title/Abstract])) OR (Risk Factor Scores[Title/Abstract])) OR (Risk Factor Score[Title/Abstract])) OR (Score, Risk Factor[Title/Abstract])) AND ((((spin*[Title/Abstract]) OR (cervical[Title/Abstract])) OR (thoracic[Title/Abstract])) OR (lumbar[Title/Abstract]))) AND (((((((((((((((((((((Strokes[Title/Abstract]) OR (Cerebrovascular Accident[Title/Abstract])) OR (Cerebrovascular Accidents[Title/Abstract])) OR (CVA (Cerebrovascular Accident[Title/Abstract]))) OR (CVAs (Cerebrovascular Accident[Title/Abstract]))) OR (Cerebrovascular Apoplexy[Title/Abstract])) OR (Apoplexy, Cerebrovascular[Title/Abstract])) OR (Vascular Accident, Brain[Title/Abstract])) OR (Brain Vascular Accident[Title/Abstract])) OR (Brain Vascular Accidents[Title/Abstract])) OR (Vascular Accidents, Brain[Title/Abstract])) OR (Cerebrovascular Stroke[Title/Abstract])) OR (Cerebrovascular Strokes[Title/Abstract])) OR (Stroke, Cerebrovascular[Title/Abstract])) OR (Strokes, Cerebrovascular[Title/Abstract])) OR (Apoplexy[Title/Abstract])) OR (Cerebral Stroke[Title/Abstract])) OR (Cerebral Strokes[Title/Abstract])) OR (Stroke, Cerebral[Title/Abstract])) OR (Strokes, Cerebral[Title/Abstract])) OR ("Stroke"[Mesh])). Literatures were screened independently by two reviewers using uniform inclusion criteria. Any disagreements should be resolved through discussion or with the assistance of a third-party researcher.

The eligibility criteria were specified using the Population, Intervention, Criteria, Outcome and Study design (PICOS) framework. The selected literatures must meet the following conditions: 1) The definition of stroke is "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin." [13,14]; 2) The original data should provide OR value and 95% confidence interval (95%CI) or the OR value and 95%CI can be calculated from the data; 3) The summary results can be expressed by corresponding statistical indicators.

Exclusion Criteria

Excluded documents should meet one of the following criteria: (1) animal studies; (2) meta-analysis and reviews; (3) duplicate studies; (4) case reports; (5) articles without available data; (6) unrelated studies.

Methodological quality evaluation. The methodological quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) scoring system. The principle of star-setting quantity was used, and the full score is 9 stars.

Statistical Analysis

Stata version 16.0 (Stata Corp LP, College Station, Texas) was used to synthesize, summarize, and evaluate the data. The collected data were tested for heterogeneity and the combined OR value and 95%CI were calculated. To determine heterogeneity across the studies, the I2 Higgins (0–100%) was adopted. The fixed-effect model was used for meta-analysis when the heterogeneity statistic I2 is less than 50%. In the meanwhile, the random-effect model was applied when the heterogeneity statistic I2 is greater than or equal to 50%. The Egger's and Begg's test was used to analyze potential publication bias when the number of articles included was more than 3. Sensitivity analysis was used to test the stability of meta-analysis results: (1) comparison of results between random effect model and fixed effect model; (2) When the number of included literatures is more than 3, the points with significant deviation from 95%CI in the funnel chart are excluded for meta-analysis, and the results are compared with those when all the literatures are included. The p value for statistical significance was set at <0.05.

Results

Study selection

According to the search terms of the literature, a total of 1706 relevant articles were initially identified. Of those articles, 110 were duplicated in databases. After screening the remaining 1518 articles using titles and abstracts, most of the studies were excluded because they were not relevant to the objectives of this study (1467), meta-analysis and reviews (78). After reading the full text of the remaining 51 articles, a total of 38 were excluded due to the inability to obtain the full text (3), the outcome variables did not match (15), research content does not meet inclusion standards (20). Finally, 13 articles were included in this study for data extraction and meta-analysis (Figure 1).

Study characteristics

The eligible studies included 6 retrospective studies and 7 case-control study. The highest NOS score was 8 and the lowest was 5. A total of 415191 patients were included in the study. The basic characteristics and NOS scores of the included studies are shown in Table 1.

Meta-analysis

According to the research contents of the included literature and the number of references for each factor, four risk factors including advanced age, hypertension, diabetes mellitus and cerebrovascular events were selected for meta-analysis.

Advanced age

Assuming advanced age as an independent factor, the results of meta-analysis using a random effect model showed that advanced age had a strong correlation with the cerebrovascular accidents (CVA) postoperatively [combined OR values=3.36, 95%CI (1.81, 6.24), P＜0.05, Figure 2]. Furthermore, mild heterogeneity was found among the studies (I2= 52.8%, P=0.12, Figure 2). After analyzing the original research, we guessed that the reasons for the mild heterogeneity might be as follows: 1. Different literatures have different definitions of advanced age (advanced age is defined as ≥65, 75 or 80, respectively); 2. The participants were ethnically diverse [9,10,12].

Hypertension

Two studies reported that the OR value between hypertension and perioperative stroke was 1.61[95%CI (1.26, 2.06)], and there was no heterogeneity between studies (I2=41.2%, P=0.192, Figure 3) [10,12]. The forest plot between hypertension and perioperative stroke is also shown in Figure 3.

Diabetes mellitus

Meta-analysis of the two included studies using random effect model showed that diabetes mellitus had a significant effect on the perioperative stroke after spine operation [OR=2.07, 95%CI (1.23,3.49), P=0.006, Figure 4 and mild heterogeneity was observed between the two studies (I2=52.7%, P=0.146) [10,12].

Cerebrovascular events

Two studies reported the relationship between cerebrovascular events and postoperative cerebrovascular accidents [9,12]. There was great heterogeneity among these studies (I2=94.3%, P＜0.01), therefore we abandoned the meta-analysis of cerebrovascular events as a risk factor for stroke after spinal surgery due to strong heterogeneity (Figure 5). We hypothesized that the strong heterogeneity may be due to the inclusion of both stroke history and transient ischemia (TIA) as cerebrovascular events.

Publication bias analysis

Using advanced age as indicators to detect publication bias, the Egger's and Begg's test results of advanced age were 0.834 and 1.000 respectively. The p value is greater than 0.05, indicating that there is little possibility of publication bias in this meta-analysis.

Discussion

This study systematically collected the studies on the risk factors of postoperative stroke after spine surgery. A total of 13 literatures were included, which clearly specified the inclusion and exclusion criteria. The statistical methods were correctly used, and the literatures quality was relatively high (all≥5 stars). Therefore, the meta-analysis results have high reliability, which showed that the advanced age, hypertension and diabetes mellitus were related to the perioperative stroke. However, cerebrovascular diseases are highly heterogeneous as risk factors for postoperative stroke. The strong heterogeneity might be due to the fact that both stroke history and transient ischemia (TIA) were included in cerebrovascular events.

Perioperative stroke is a relatively rare disease9, and there are not many literatures reported on it in clinical practice, even fewer literatures meeting our inclusion criteria. Older age, hypertension, and diabetes have been reported in two or more literatures as risk factors. However, coagulation abnormalities, history of heart disease, operation time, length of hospital stay, OPLL, COPD, and stroke history, etc cannot be included in the meta-analysis due to the lack of sufficient original studies [9-12,15,16]. This meta-analysis showed that advanced age, hypertension and diabetes mellitus are risk factors for stroke after spinal operation.

As one of the risk factors, old age has been reported in three literatures, with OR values of 5.56, 2.138 and 2.5 respectively. The elderly, as a predisposed group for the disease, often present with other basic diseases and are at high risk of developing postoperative stroke [17,18]. In addition, it has been reported that increasing age is associated with atherosclerosis. Old age was the most robust risk factor for subclinical atherosclerosis [19]. Patients with diabetes exhibit accelerated progression of carotid intima–media thickness and atherosclerotic plaque formation, and are prone to occlusive disease affecting small penetrating arteries in the brain [20]. Furthermore, diabetes increases cerebral edema, neovascularization, and protease expression that may damage endothelial integrity [21]. All these mechanisms may lead to the occurrence of stroke. In addition, Chronic hypertension may lead to stroke through injury of endothelial cells and thickening of smooth muscle cell [22]. These changes likely impair blood flow autoregulation and contribute to the increased infarct size after vessel occlusion [23].

For cerebrovascular events, this meta-analysis combined TIA with stroke as cerebrovascular events and found that there was extremely strong heterogeneity. We speculate that the possible reason is that TIA and stroke have different definitions. Transient ischemic attack, as a warning event for future stroke, is a less severe disease. However, according to previous literatures, both TIA and stroke can increase the incidence of postoperative stroke after the spinal operation (OR=2.83, 146.046 respectively) [10,12]. Therefore, more original studies are required to further investigate the association between history of cerebrovascular disease and stroke after spinal surgery. To our knowledge, this is the first meta-analysis of risk factors for stroke after spinal surgery. Chronic diseases such as diabetes, hypertension, or advanced age may have increased vascular fragility, which in turn makes the probability of stroke increasing. However, more original studies were required to further investigate the association between the above risk factors and stroke after spinal surgery in the future.

Conclusions

Up to now, the risk factors for stroke after spinal surgery are still controversial. This meta-analysis is conducted to investigate risk factors for stroke after spinal operation. The results shows that advanced age, hypertension and diabetes mellitus are the current risk factors for postoperative cerebrovascular accidents. We believe that the results of this study can provide clinical reference for the risk factors of stroke after spinal surgery.

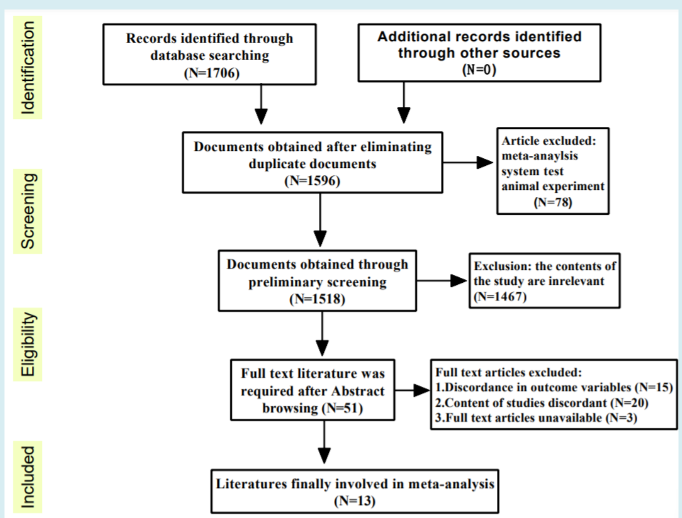

Figure 1: Flow chart of the searched, identified and included studies for meta-analysis.

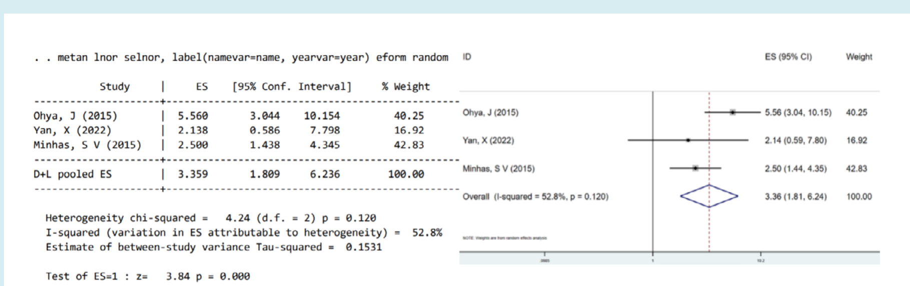

Figure 2: Multivariate analysis of advanced age in a forest map.

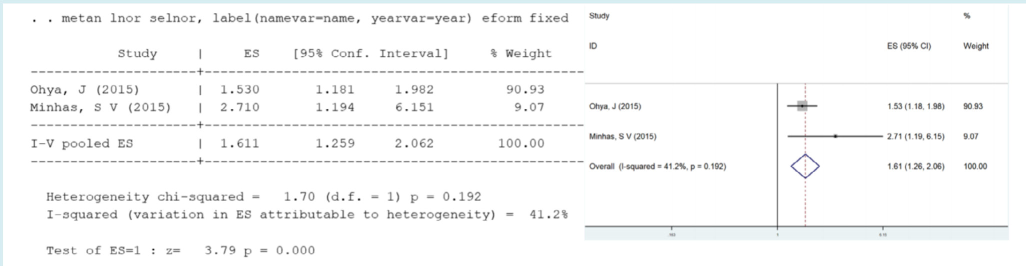

Figure 3: Multivariate analysis of hypertension in a forest map.

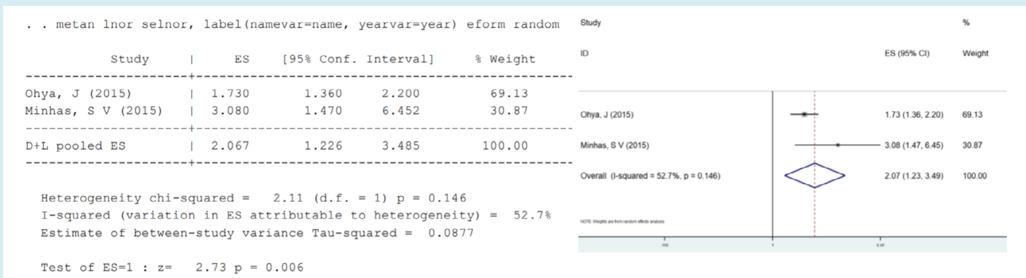

Figure 4: Multivariate analysis of diabetes mellitus in a forest map.

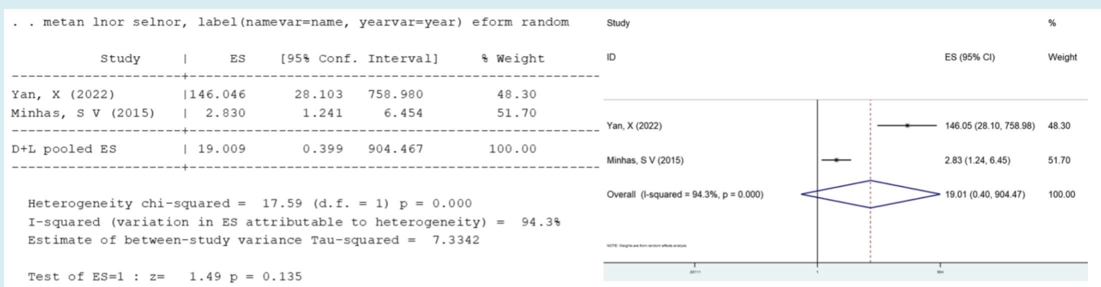

Figure 5: Multivariate analysis of cerebrovascular events in a forest map.

Author, year	Study design	Date of data collection	Sample(N)	Mean age (years)	Male (N or %)	risk factors	Statistical method	NOS scores
Bronheim, R S 2018	retrospective study	2006-2013	9295	61.01	4146	1. coagulopathy	Logistic regression analysis	5
Arrighi-Allisan, A E 2020	retrospective study	2008-2016	3226	63.1	1534	1. diabetes mellitus (P=0.576)	Logistic regression analysis	7
Wu, J C 2012	Prospective study	2004-2007	30866	40.48±12.74	76.40%	1. spinal cord injury	Logistic regression analysis	6
Huang, L C 2015	Prospective study	2000-2009	13503	67	5099	1. spinal surgery	Logistic regression analysis	6
Wu, J C 2012	Prospective study	2000-2005	18135	57.9	10576	1. spinal surgery	Logistic regression analysis	7
Labaran, L A 2019	retrospective study	2006-2013	30547	unknown	19020	1. polycythemia vera (P=0.580)	Logistic regression analysis	5

Ohya, J 2015	retrospective study	2007-2012	167106	unknown	98445	1. age (≥80) 2. heart disease 3. diabetes mellitus 4. hypertension 5. spinal surgery 6. teaching hospital 7. length of stay	Logistic regression analysis	8
Yan, X 2022	retrospective study	2015-2021	17408	unknown	8586	1. stroke history 2. age (≥65) (P=0.250) 3. hyperlipidemia (P=0.027)	Logistic regression analysis	8
Shin, J 2019	retrospective study	2002-2015	7450	unknown	3810	1. OPLL	Logistic regression analysis	5
Lin, S Y 2018	Prospective study	2000-2010	27990	54.9±13.4	11423	1. cervical spondylosis	Logistic regression analysis	6
Arena, P J 2020	Prospective study	2007-2018	43063	unknown	20563	1. diabetes mellitus 2. stroke history	Logistic regression analysis	7
Wu, J C 2012	Prospective study	2000-2005	4452	unknown	1793	1. spinal surgery (P=0.522)	Logistic regression analysis	6
Minhas, S V 2015	retrospective study	2006-2012	42150	unknown	16779	1. age (≥75) 2. diabetes mellitus 3. hypertension 4. transient ischemic attack 5. dyspnea 6. COPD 7. operation time	Logistic regression analysis	7

Table 1: Characteristics and quality evaluation of the included studies.
Legend: The basic characteristics and NOS scores of the included studies.

- **Declarations**
  Ethics approval and consent to participate: Not applicable
  Consent for publication: Not applicable
  Availability of data and materials: The datasets of the current study are available from the corresponding author upon reasonable request
  Competing interests: The authors declare that they have no competing interests

- **Funding**
  There is no source of funding for research and/or publication

- **Authors' contributions**
  HY designed this study. LX analyzed the data and drafted the paper. ZT, SH revised the manuscript. SH provided critical comments on this draft. All authors read and approved the final manuscript.

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  Not applicable

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